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REVIEW

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Gut microbiota determines the fate of dietary fiber-targeted interventions in host health

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ABSTRACT

Epidemiological investigation confirmed that the intake of dietary fiber (DF) is closely related to human health, and the most important factor affecting the physiological function of DF, besides its physicochemical properties, is the gut microbiota. This paper mainly summarizes the interaction between DF and gut microbiota, including the influence of DF on the colonization of gut microbiota based on its different physicochemical properties, and the physiological role of gut microbiota in destroying the complex molecular structure of DF by encoding carbohydrate-active enzymes, thus producing small molecular products that affect the metabolism of the host. Taking cardiovascular disease (Atherosclerosis and hypertension), liver disease, and immune diseases as examples, it is confirmed that some DF, such as fructo-oligosaccharide, galactooligosaccharide, xylo-oligosaccharide, and inulin, have prebiotic-like physiological effects. These effects are dependent on the metabolites produced by the gut microbiota. Therefore, this paper further explores how DF affects the gut microbiota's production of substances such as short-chain fatty acids, bile acids, and tryptophan metabolites, and provides a preliminary explanation of the mechanisms associated with their impact on host health. Finally, based on the structural properties of DF and the large heterogeneity in the composition of the population gut microbiota, it may be a future trend to utilize DF and the gut microbiota to correlate host health for precision nutrition by combining the information from population disease databases.

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Dietary fiber; gut microbiota; metabolism; host health; precise nutrition

1. Introduction

The World Health Organization (WHO) and national nutritional communities have given a uniform recommendation for dietary fiber (DF) intake of between 25–35 g per person per day. Increasing DF consumption or replacing refined grains with whole grains can reduce the morbidity and mortality of diseases such as type 2 diabetes, cardiovascular disease, breast cancer, colorectal cancer, and other diseases. However, most people are far from meeting this requirement[1]. The human body can't digest DF, but the intestinal microbiota genome utilizes different DFs by encoding a large number of carbohydrate-active enzymes (CAZymes),[2] and produces metabolites. A large body of evidence suggests that the intestinal microbiota and its metabolites influence host health through the gut-organ axis.[3] However, the structure, viscosity, and other physicochemical properties of DF specifically affect the colonization of the intestinal microbiota. There is some public consensus that dietary fiber produces health benefits, and the gut microbiota and its metabolites are a hot topic affecting human health. However, given that previous reviews on DF impacting host health have described the contribution of DF to the gut microbiota and its metabolite production. For example, Kassem Makki et al. reviewed the impact of DF on gut microbial ecology, and the significance of microbial metabolism of DF to produce short-

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chain fatty acids (SCFAs) on the immune system and gastrointestinal diseases.[4] Gill SK et al. described the role of DF in gastrointestinal disorders by considering the contribution of its physicochemical properties in micronutrient utilization, intestinal transit time, fecal formation, and microbial specificity.[5] Therefore, when exploring the interactions between DF and the gut microbiota as well as host health in this paper, the focus is on the interactions between the gut microbiota and DF (firstly, the physicochemical properties of DF influence the colonization of the microbiota in the gut, and secondly, the gut microbiota goes on to utilize the DF by encoding a large number of carbohydrate-active enzymes with specific properties, including through bacterial cross-feeding), and the impact of metabolites produced by gut microbes utilizing DF on specific diseases, and the mechanisms are explored in greater depth. Specifically, this paper takes DF as the research object, taking cardiovascular diseases, liver diseases, and immune diseases as examples, and comprehensively summarizes DF as a potential microbiota-directed food (through the relationship between diet and gut microbiota and gut microbiota and disease, replacing food ingredients in the daily diet with substances that help to stimulate the growth of beneficial microbiota, thus enhancing the importance of intestinal flora in the treatment of disease), how to stimulate the propagation and growth of specific probiotic bacteria and produces SCFAs, bile acids (BAs), tryptophan metabolites and other substances to affect the health of the host through specific ingredients.

1.1. Definition and classification of DF

DF was first put forward by Hipsley. At that time, the term only referred to indigestible food components, such as lignin, cellulose, and hemicellulose.[6] With the use and exploration of later generations, the definition of DF has also been modified and improved based on its structure and physiological function. Historically, it was thought that fiber was composed of polysaccharides (degree of polymerization [DP] >10), which were not easy to digest and absorb in the small intestine but fermented in the large intestine in whole or in part.[7] The Codex Alimentarius Commission revised the definition of DF to include short-chain carbohydrates with DP values of 3–9, but not all countries accept oligosaccharides as a component of DF.[8] The European Food Safety Authority defines DF as indigestible carbohydrates and lignans and classifies them as[9]:

- nonstarch polysaccharides – cellulose, hemicelluloses, pectins, hydrocolloids (i.e., gums, mucilages, β-glucans).
- resistant oligosaccharides – fructo-oligosaccharides (FOS), galacto-oligosaccharides, and other resistant oligosaccharides.
- resistant starch.
- lignin is associated with dietary fiber polysaccharides.

2. DF interacts with the gut microbiota

2.1. Effects of physicochemical properties of DF on the gut microbiota

As shown in Table 1, the physicochemical properties of DF vary with different structural components. For instance, cellulose cannot be dissolved in water, but pectin and hydrocolloid can be dissolved. Although resistant oligosaccharides are also easy to dissolve, they can't form high-viscosity solutions like guar gum and mucilage. Similarly, resistant starch is not easy to be dissolved and digested because of its physical form and cell structure.[8] As the physicochemical properties of DF, water retention capacity, viscosity, binding capacity, swelling capacity, and fermentation capacity are very important for the physiological role of DF.[24] Based on solubility, DF has been classified as insoluble dietary fiber (IDF) composed of plant cell wall components (such as hemicellulose, lignin, and cellulose) and soluble dietary fiber (SDF) composed of non-cellulosic polysaccharides (such as gum and pectin). IDF is characterized by its porous nature and low density, which can effectively shorten intestinal transit time and increase fecal bulk to prevent and improve constipation through the formation of particles and water-holding capacity.[25]

In addition to particle formation and water-holding capacity, IDF is also theoretically an

Table 1. Classification and physicochemical characteristics of DF.

		Physicochemical characteristics				
Classification	Fiber type	Monosaccharide components	Glycosidic linkage	Solubility	Fermentability	Reference
Non-digestible oligosaccharides	Fructo-oligosaccharides	Glucose, Fructose	β-2,1	High	High	10
	Galacto-oligosaccharides	Glucose, Galactose	β-1,3; β-1,4; α-1,6	High	High	10
Non-starch polysaccharides	Cellulose	Glucose	β-1,4	Insoluble	Low	11
	β-Glucan	Glucose	β-1,3; β-1,3/β-1,4; β-1,6	Low to medium	High	12
	Pectins	Galacturonic acid, rhamnose, galactose, arabinose	α-1,4	High	High	13
	Mucilages	Galactose, arabinose	β-1,4; β-1,3; α-1,3	High	High	14
	Gums	Arabinose, galactose, rhamnose, etc.	β-1,4; α-1,6	High	High	15
	Arabinoxylans	Arabinose, xylose	α-1,3; β-1,4; β-1,3	Low to high	High	16 17
	Arabinogalactans	Arabinose, galactose	β-1,3; β-1,6; α-1,3; α-1,4	Medium	High	18
	Galactomannans	Mannose, galactose	β-1,4; α-1,6	Medium to high	High	19
	Inulin	Ribofuranose, pyranosides	β-2,1	Medium to high	High	20
	Alginate	Mannuronic acid; glucuronic acid	α-1,4	Insoluble to high	High	21
	Methylcellulose	Synthesized		High	Non-fermentable	22
Resistant Starch	RS1 (physically inaccessible)	Glucose	α-1,4; α-1,6	Insoluble	High	11 23
	RS2 (starch conformation)	Glucose	α-1,4; α-1,6	Low	High	
	RS3 (retrograded)	Glucose	α-1,4; α-1,6	Low	High	
	RS4	Chemical and physical modification		Low to High	High	
	RS5 (starch – lipid complex)	Synthesized (e.g. amylose-stearic acid complex)		Low	Low	23
Other	Lignins	Polymer cross-linked phenyl propane		Insoluble	Low	11

excellent biofilm-forming substrate because of its matrix's small particle size, rough surface, and large specific surface area. Bacterial biofilms are bacterial communities with complex surface-attached, which are mainly composed of extracellular DNA, secreted protein, and polysaccharides.[26] In the intestinal tract, the presence of biofilm can provide a stable growth environment and a protective ecological niche for bacteria within the barrier, increasing their competitive advantage, and can also assume the functions of material transportation and information transfer. The formation of biofilm in healthy intestinal flora is conducive to the promotion of synergistic effects between bacteria and bacteria and between bacteria and host.[27] Beneficial biofilms can effectively adapt to food matrices and help microbes tolerate adverse environmental conditions. These matrices can be used as natural scaffolds for bacterial cells to attach to and grow into biofilm. For example, *Lactobacillus spp*. have higher bioactivity when they form a film on a wheat bran substrate.[28] Through the successful colonization of resistant starch fibers in chickpea milk, the wild-type cells of *Bacillus subtilis* also showed stronger viability and greater tolerance to environmental stress.[29] Due to its porous structure, grape seed powder can be used as a carrier to promote the formation of strong biofilms for *Bifidobacterium breve*, *Bifidobacterium pseudo, Bifidobacterium longum*, and weak biofilms for *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, and *Bifidobacterium animalis* by adsorption of cells.[30] *Bifidobacterium bifidum* cells adhere to the surface of wheat fibers and secrete extracellular material to form a biofilm.[31] In turn, pathogenic bacterial biofilms can provide a protective environment for pathogens, evading host immunity, destroying intestinal epithelial cells, and promoting wound infection, leading to deterioration. Compared with the studies on the prophylaxis and treatment of harmful biofilm, there is less research on promoting the formation of beneficial biofilm.[26]

It is believed that SDF increases viscosity. Not all SDF have high viscosity. Highly branched, bush-like polymers with multiple irregularly spaced

branches that cannot be arranged into regular arrays have no great impact on viscosity and are called non-viscous (e.g., wheat dextrins, oligofructose, and inulin); Correspondingly, straight-chained or linear polymers can be arranged regularly, and the length of linear chains is positively related to the degree of viscosity. Linear polymers formed by cross-linking adjacent chains can form gels such as raw guar gum, β-glucan, and psyllium.[32] Highly viscous aqueous solutions or gels thicken the contents of the intestinal lumen, slowing the migration of nutrients to the intestinal wall. As a result, they reduce the absorption of cholesterol, sugar, and other nutrients to lower blood sugar and plasma cholesterol.[11]

For example, nutrient absorption can occur throughout the small intestine, while bile, which aids in the digestion and absorption of lipids, is limited to the end of the ileum where it is reclaimed for further recycling. As the gelatinous fiber passes through the small intestine, water is absorbed making it thicker and less fluid, thus trapping the bile and delaying and interfering with its reabsorption.[32] In addition, due to its viscosity, the gel seems to react more like a solid than a liquid in the gastrointestinal tract, causing the stomach to swell, increasing satiety, and delaying gastric emptying.[33]

The degree to which fibers are fermented varies. For example, lignin is not fermented, while pectin can be almost completely fermented. Compared with IDF, SDF is more easily fermented by colon bacteria.[11] Fermentable fibers are fermented in the colon to promote the growth of intestinal and fecal microflora and increase the content of by-products of microbial metabolism such as SCFAs and gases, which are helpful to increase the volume of feces and maintain the integrity of colon cells and other physiological functions.[8] Gases mainly hydrogen (H_2), carbon dioxide (CO_2), and methane (CH_4) can be produced in the intestines of healthy people in amounts of 0.2–1.5 L/d.[34] For example, when inulin is fermented in vivo, the concentration of SCFAs increases and the abundance of *Parabacteroides* rises,[35] and *Parabacteroides* can produce H_2 and CO_2.[34] H_2 is considered a bioactive gas with antioxidant, anti-apoptotic, anti-inflammatory, cytoprotective and signaling properties.[36] In addition, hydrogen-rich microorganisms such as acetate-reducing bacteria and sulfate-reducing bacteria, in turn, can convert H_2 into acetate and hydrogen sulfide (H_2S). Endogenous H_2S has an anti-inflammatory effect on colonic pain. It can promote ulcer healing through its action on the smooth muscle, but the excess gas produced also causes side effects such as abdominal distension and abdominal pain.[37]

Water retention capacity and swelling capacity as two important aspects of DF for constipation relief. DF with higher water retention and swelling capacity can increase the volume of human feces, promote intestinal peristalsis, and reduce the residence time of feces in the intestine.[38] However, there is a common misconception here that not all DF with these two abilities have laxative or regularity benefits.[39] Large, coarse wheat bran relieves constipation, but processed, small, smooth wheat bran particles may cause constipation. This is because insoluble particles have a mechanically stimulating effect on the mucous membranes of the large intestine, stimulating the secretion of water and mucus as a defense mechanism against abrasion (Cutting the plastic to match the size and shape of the bran pellets found that the plastic had the same constipation-relieving effect).[32] In contrast, finely ground bran increases the dry weight of the feces and reduces its water content, resulting in harder stools.[32 39] However, in a study on the kinetics of gastrointestinal tract emptying in mice by bran IDF with different particle sizes, it was found that the particle size of bran IDF was reduced by ultra milling.[40] Reducing the particle size of IDF increased its specific surface area. The large specific surface area exposed more hydrophilic sites, increasing the water retention capacity of the DF, decreasing the viscosity, and improving the gastrointestinal emptying capacity.[38 40] Gelatinous SDF has a high water-holding capacity, which can prevent dehydration and leads to an increase in fecal water content, which produces bulkier, softer, and easier-to-discharge stools. However, many gel-forming soluble fibers (such as xanthan gum, guar gum, and beta-glucan) are easily fermented in the colon, resulting in the loss of their gel properties and water-retaining capacity, however, unfermented gel-like psyllium relieves constipation. Thus, both of these constipation-relieving mechanisms require that DF must exist in feces and resist

fermentation.[32] However, in a study screening efficient cellulose-degrading strains, it was found that the microstructure of fermented tea residue SDF was fluffy and porous, with a significant increase in water retention capacity, and that the loose and porous structure was more conducive to water molecules penetrating into the interior and avoiding water molecules escaping.[41] The reason for such two controversies may be the heterogeneity of in vivo and in vitro, mouse and human studies, and the treatment would need to take into account the particle size of DF in different situations, the amount of intake, and even the degree of fermentation of DF under conditions of different intestinal microenvironments (pH, intestinal microorganisms, etc.), as well as the differences between diseased (constipated) states and normal healthy individuals.[39–41] Second, while animal models of DF tend to be more effective in preventing and mitigating inflammatory diseases, the amount of fiber used in animal versus human clinical trials is also much higher, with prebiotics in particular often being dosed at up to 40 times higher than body weight doses.[42] Even a dose of DF that meets today's dietary recommendations (30 g/day) is still far less than the amount of fiber we consume when we form symbiotic relationships with microbes.[4] For this reason, some researchers recommend consuming more than 50 grams of DF per day.[43]

2.2. Utilization of DF by the gut microbiota

Salivary α-amylase breaks down these α-1,4 glycosidic bonds to produce shorter polysaccharides when the body digests foods rich in straight-chain and branched-chain starches. After the shortened polysaccharide reaches the small intestine, it is decomposed by the complex of pancreatic amylase and enzyme on the plasma membrane of mucosa, and absorbed from the lumen of the small intestine via specialized transport proteins; In contrast, the monosaccharide molecules of structural carbohydrates, such as cellulose, consist of glucans linked by β-D-(1 → 4) glycosidic bonds.[38] The human body lacks β-glucosidase, so digestion can only be carried out in the large intestine by symbiotic bacteria secreting CAZymes. Monosaccharides produced by digestion can be used by microorganisms on the one hand, and absorbed by special transporters at the top of colon cells on the other.[44] DF, a nutrient class containing large amounts of polysaccharides that cannot be digested by human enzymes, provides an important substrate for microorganisms living in the distal intestine. There are 17 kinds of enzymes in the human gastrointestinal tract that can digest most starch, but the intestinal microflora is not the same. They have thousands of CAZymes with different specificity, which enable them to depolymerize polysaccharides and ferment them into SCFAs that can be absorbed by the host.[45] The main microorganisms that degrade DF are Firmicutes and Actinobacteria.[46] These CAZymes are composed of Glycoside Hydrolases (GHs), Glycosyltransferases (GTs), Polysaccharide Lyases (PLs), Carbohydrate Esterases (CEs), and Auxiliary Active enzymes (AAs).[47] GHs can be divided into exo-glycoside hydrolase and endo-glycoside hydrolase according to their cleavage sites in carbohydrate substrates, which are responsible for catalyzing the hydrolysis of glycosidic bonds in various carbohydrate substrates. GTs form glycosidic bonds by activating donors and transfer sugars to specific receptors (e.g., lipids, proteins, and other glycans) by activating donors to form glycosidic bonds. Polysaccharide containing uronic acid is the substrate of PLs, among which glycosaminoglycan is one of the most common substrates of PLs in human gut flora; CEs catalyze the de-esterification of various carbohydrate substrates; AAs is a collection of redox-active enzymes, which act on carbohydrates; In addition, Carbohydrate-binding modules (CBMs) are catalytically inactive structural domains, which are usually attached to CAZymes, bind a series of carbohydrate motifs of different compositions and sizes and help the associated CAZymes to direct to the substrate.[2] Taking pectin as an example, pectin consists of a main chain containing a large amount of galacturonic acid (GalA) and a variety of side chains containing nearly 17 different monosaccharides and more than 20 different bonds. The complex structure of pectin means that its depolymerization needs more hydrolase, lyase, and esterase. Pectinases are present in families GH28, GH88, GH105, PL1, PL2, PL3, PL4, PL9, PL10, PL11, and PL15.[48] PLs and GHs cut the O-bond (C_1-O-C_n) between the main chain and the side chain of pectin, while CEs are responsible for removing methoxy/acetyl groups from pectin.[49]

Table 2. DF, gut microbiota, CAZymes, disease, and metabolites.

Gut Microbiota and DF	CAZymes Family Number		Associated disease	Metabolite
Bacteroides stercoris	GHs:	2, 3, 9, 13, 18, 20, 23-25, 27-29, 31, 32, 36, 43, 53, 57, 63, 65, 73, 76, 77, 88, 92, 95, 97, 105, 106, 109, 117, 125, 130, 133, 144, 171	Non-alcoholic Fatty Liver Disease[53]	BCAAs[53]
Resistant starch ↓ [53]	GTs:	2-6, 8, 11, 19, 26, 28, 30, 35, 51, NC;	Inflammatory Bowel Diseases[54]	SCFAs[55 56]
	PLs:	1, 8, 10-13, 15, 21, 20, 33, 37;		
	CEs:	4, 7, 8, 9, 11, 12, 20, NC;		
	CBMs:	20, 48, 50, 58, 91, 93	Cardiovascular Diseases[55]	–
Faecalibacterium prausnitzii	GHs:	1-3, 13, 23, 25, 28, 31, 32, 77, 94, 105, 112, 172	Atherosclerosis[58]	LPS & SCFAs[58]
Inulin & pectin ↑ [57]	GTs:	2, 4, 5, 26, 28, 32, 35, 51, 116, NC	Ulcerative Colitis[54 57]	SCFAs[57]
	CEs:	4, 8, 9		
	CBMs:	13, 48, 50	Prehypertension[59]	SCFAs[59]
Bacteroides uniformis	GHs:	2, 3, 5, 9, 13, 15, 16, 18, 20, 23-26, 28-33, 35, 36, 38, 42, 43, 51, 53, 55, 57, 63, 65, 66, 73, 74, 76-78, 84, 88, 92, 94, 95, 97, 105, 108, 109, 115-117,125, 127, 130, 133, 144, 154, 158, 171, 172, 182, 183, NC	Inflammatory Bowel Diseases[56]	SCFAs[56]
Inulin↑ [60]				
Insoluble β-1,3-glucan↑ [61]	GTs:	1-5, 9, 11, 14, 19, 20, 26, 28, 30, 32, 35, 51, NC	Prehypertension[62]	–
	PLs:	8, 27, 30, 38, 42		
	CEs:	4, 7, 11, 12, 20, NC	Hypertension[62]	–
	CBMs:	6, 20, 32, 35, 38, 48, 50, 57, 62, 67, 91, 98		
Bacteroides thetaiotaomicron	GHs:	2, 3, 13, 16, 18, 20, 23-25, 28-33, 35, 36, 38, 42, 43, 51, 53, 57, 66, 73, 76-78, 84, 88, 89, 92, 95, 97, 99, 105, 106, 109, 110, 115, 123, 125, 127, 130, 133, 137-144, 146, 147, 154, 163, 171, 182, NC	Nonalcoholic fatty liver disease[65]	Unsaturated fatty acids[65]
Arabinose, pectin,	GTs:	1-5, 9, 14, 19, 26, 28, 30, 32, 35, 51, 101, NC	Alcohol-related liver disease[66]	BAs[66]
Arabinan ↑ [63]	PLs:	1, 8-13, 15, 26, 27, 29, 33, 40, 42, NC		
β-glucan[64]	CEs:	2, 4, 6-9, 11, 12, 19, 20, NC	Inflammatory Bowel Diseases[54]	SCFAs[67]
	CBMs:	6, 13, 20, 32, 35, 50, 51, 57, 58, 62, 91, 93, 97, NC	Cardiovascular Diseases[64]	Indole-3-lactic acid, indole-3-acetic acid, kynurenine [64]
Bacteroides xylanisolvens	GHs:	2, 3, 5, 10, 13, 16, 18, 20, 23-33, 35, 36, 38, 42, 43, 50, 51, 57, 66, 67, 73, 76, 78, 88, 89, 92, 95, 97, 99, 105, 106, 109, 110, 115, 123, 125, 127, 130, 133, 137-144, 146, 163, 165, 171, 172, 182, NC	Cardiovascular Diseases[64]	Indole-3-lactic acid, indole-3-acetic acid, kynurenine [64]
Xylan ↑ [68]	GTs:	1-5, 9, 11, 14, 19, 26, 28, 30, 32, 35, 51, NC		
β-glucan[64]	PLs:	1, 8, 10, 12, 13, 15, 29, 33, 35, 40, 42, NC	Nonalcoholic fatty liver disease[69]	Folate[69]
	CEs:	4, 6, 7, 9, 11, 12, 15, 19, 20, NC	Ulcerative Colitis[70]	–
	CBMs:	4, 6, 20, 32, 35, 48, 50, 57, 62, 91, 93, 97, NC		
Parabacteroides distasonis	GHs:	2, 3, 13, 15, 16, 20, 23, 24, 26, 27, 29, 30, 31-33, 35, 36, 38, 43, 51, 57, 63, 73, 76-78, 84, 92, 95, 97, 109, 110, 123, 125, 127, 130, 133, 140, 144, 171, 172, 177, NC	Nonalcoholic fatty liver disease, Obesity[73]	Succinate & BAs[73]
Inulin ↑ [71]	GTs:	1-6, 8, 9, 11, 14, 19, 20, 26, 28, 30, 32, 35, 51, NC		
Resistant starch ↑ [72]	PLs:	12, NC	Ulcerative Colitis, Colorectal Neoplasms[74]	SCFAs[74]
	CEs:	4, 9, 11, 20		
	CBMs:	20, 32, 35, 48, 50, 51, 62, 67, 91, 93		
Bacteroides intestinalis	GHs:	2, 3, 5, 8-10, 13, 16, 18, 20, 23, 25-33, 35, 36, 38, 39, 42, 43, 50, 51, 53, 55, 57, 63, 65-67, 73, 76-78, 88, 89, 92, 95, 97, 105, 106, 109, 115, 116, 123, 125, 127, 130, 133, 144, 146, 147, 154, 171, 172, 182, 184	Obesity and Hyperlipidemia[78]	BAs[78]
Arabinoxylans ↑ [75]				
Xylan ↑ [76]	GTs:	1-5, 8, 11, 14, 19, 28, 30, 35, 51, NC	Inflammatory Bowel Diseases[54 77]	Lactate[77]
Laminaran[77]				
	PLs:	1, 6, 8, 10-13, 15, 17, 21, 26, 33, 35, 37, 38, 40, 42	Hypertension [–]	–
	CEs:	2, 4, 6-8, 11, 12, 15, 20, NC	Cardiovascular Diseases[–]	–
	CBMs:	4, 6, 13, 20, 32, 35, 38, 48, 50, 51, 57, 62, 67, 91, 93, 96, 98, NC		

(*Continued*)

Table 2. (Continued).

Gut Microbiota and DF		CAZymes Family Number	Associated disease	Metabolite
[Ruminococcus] torques Resistant starch ↓ [79]	GHs:	1, 2, 4, 13, 18, 20, 23, 25, 29, 31, 33, 36, 42, 51, 73, 77, 84, 89, 95, 101, 112, 123, 136	primary biliary cirrhosis[80]	BAs[80]
	GTs:	2, 4, 5, 26, 28, 35, 51, NC	Non-alcoholic fatty liver Disease[81]	–
	CEs:	4, 9	Colorectal Neoplasms[82]	–
	CBMs:	13, 32, 34, 40, 48, 50, 51, NC	Crohn's Disease[81]	–
Roseburia intestinalis Xylan ↑ [76] β-mannans ↑ [83]	GHs:	1-3, 5, 8, 10, 13, 18, 20, 23-29, 31, 32, 35, 36, 38, 39, 42, 43, 51, 53, 65, 73, 74, 77, 78, 85, 88, 94, 95, 105, 112, 113, 115, 120, 125, 127, 130, 133, 136, 166, 172, NC	Ulcerative Colitis[84]	SCFAs[84]
	GTs:	2, 4, 5, 11, 23, 26, 28, 35, 51, 111, 113, NC	Intrahepatic cholestasis of pregnancy[85]	BAs[85]
	CEs:	2, 4, 8, 9, 12, 17	Colorectal cancer[86]	SCFAs[86]
	CBMs:	6, 9, 22, 23, 27, 32, 34, 48, 50, 61, 82, 86, 91	Cardiovascular Diseases[62]	–

Arrows in the table indicate the effect that this type of dietary fiber may have on the abundance of this gut microorganism. The gut microbiota listed in the table have an effect on specific diseases and this effect may depend on the corresponding metabolites."–" indicates that no relevant literature support was found at this time. CAZymes: carbohydrate-active enzyme; GHs: Glycoside Hydrolases; GTs: GlycosylTransferases; PLs: Polysaccharide Lyases; CEs: Carbohydrate Esterases; CBMs: Carbohydrate-Binding Modules; BCAAs: branched-chain amino acids; SCFAs: short-chain fatty acids (SCFAs); LPS: lipopolysaccharide; BAs: bile acids.

Combined with GMrepo database[50 51] and CAZymes database,[52] Table 2 lists some intestinal microorganisms that may interfere with cardiovascular diseases, liver diseases, kidney diseases, and gastrointestinal diseases, and further summarizes the sequences of the CAZymes of polysaccharides utilized by these gut microbes, as well as some metabolites that have been proved to interfere with the above diseases.

The utilization of DF by the intestinal microbes is also closely related to its source, molecular structure, particle size, combination with other compounds, and other physical and chemical properties mentioned above. Particle size determines the sensitivity of gut microbes to binding, digestion, intestinal transit time, and water retention; Water retention affects the ability of bacteria to penetrate and digest DF.[46] Based on the above arguments, intestinal microorganisms encoding different CAZymes metabolize DF with different structures and physical and chemical properties, and then produce various metabolites, which migrate to different tissues and parts of the human body, combine with other substances or directly activate various pathways to play a role, and finally alleviate or induce the occurrence of diseases.

3. Gut microbiota metabolites intervene in host health

A fiber diet can change the microbial composition and regulate the production of metabolites, which are likely to be the key substances for targeted intervention in host health. Numerous scholars have explored the effects of metabolites on host health through the combination of metabonomics and other genomics, and proved that most metabolites do have different effects in the face of different diseases, and even have the opposite effect. For example, TMAO with high circulation in the blood is thought to promote the development of atherosclerosis through various mechanisms,[87] but when it acts on pancreatic ductal adenocarcinoma (PDAC), it can drive the immune activation of PDAC to inhibit tumor growth.[88] Patients with IBS are restricted from eating foods rich in FODMAPs to avoid the fermentation of intestinal microflora to produce more intestinal gas.[89] However, exogenous H_2 administered in the form of bubble water to the intestines of drug-induced Parkinson's animals can improve Parkinson's symptoms.[36] Therefore, targeting microbial metabolic function through specific DF intervention is a key adjustable factor affecting host health. As SCFAs, BAs, and tryptophan metabolites have been extensively studied and shown to modify outcomes in a wide range of diseases, their roles are closely linked to involvement in various metabolic pathways and are therefore highlighted below.

3.1. Gut microbiota ferment DF to generate SCFAs

SCFAs are a kind of saturated fatty acid composed of one to six carbons produced by glycolysis fermentation of carbohydrates that escape digestion and absorption in the small intestine, among them, acetate (C2), propionate (C3) and butyrate (C4) are the most abundant. Besides these three kinds, it also includes formic acid, valeric acid, caproic acid, and other branched-chain fatty acids (BCFAs).[90] Depending on diet, many studies have pointed out that the concentration of SCFAs varies in different parts of the body, for example, its concentration can reach 70 ~ 140 mm in the proximal colon, but it may only be 20 ~ 70 mm in the distal colon,[91] and the molar ratio of acetate: propionate: butyrate in the colon is approximately 60:20:20.[92]

As shown in Figure 1, DF is usually first degraded extracellularly to produce monosaccharides such as pentose and hexose. These monosaccharides are then utilized by the microorganism and converted into pyruvate through the Embden-Meyerhof pathway. If *Bifidobacterium* exists, it can also be converted into pyruvate through the pentose phosphate pathway. Pyruvate produced by these two pathways is converted into acetyl coenzyme A, lactate, and/or succinate through a series of reactions. Acetyl coenzyme A produces the byproduct CO_2 and formate may be further converted to acetate.[44] Acetic acid-producing bacteria (e.g., *Blautia hydrogenotrophica*)[93] also produce acetyl coenzyme A by reducing CO_2 molecules using the Wood-Ljungdahl pathway.[94]

There are three pathways by which colon bacteria form propionate: the propanediol pathway, the acrylate pathway, and the succinate pathway.[95] The succinate pathway processes most

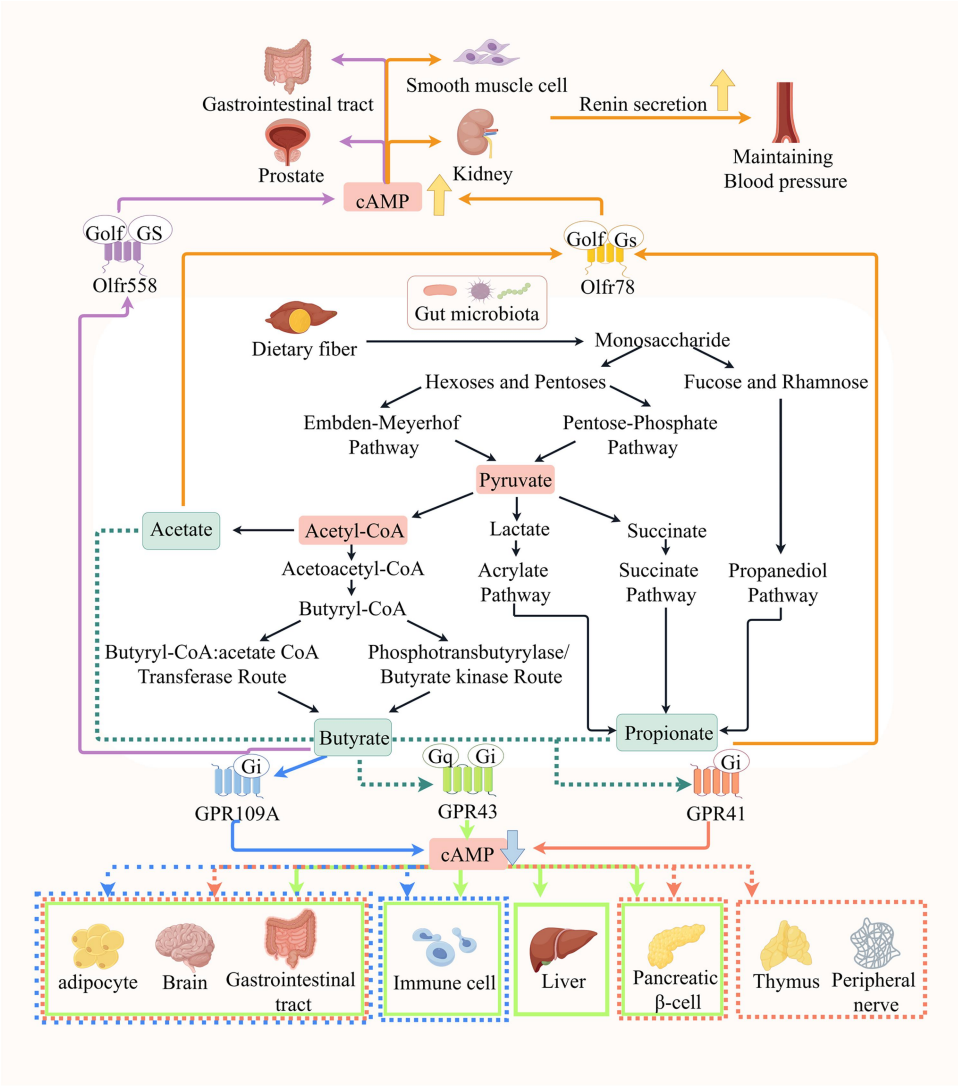

Figure 1. SCFAs affect host health. Intestinal microflora ferments DF to form SCFAs. Propionate, acetate, and butyrate, as ligands of Gpr41 and Gpr43, activate Gpr43 to bind with Gi and Gq proteins, and Gpr41 to bind with Gi proteins, thus inhibiting cAMP, participating in leptin secretion by adipocytes and suppressing appetite; L cells involved in intestinal endocrine produce PYY and GLP-1, reduce food intake, inhibit glucagon secretion and gastric emptying; GRP41 also acts on the thymus to promote Treg cells differentiation; It acts on the peripheral and central nervous system, activates the expression of IGN gene, mediates the brain's regulation of previously ingested food and blood sugar, and maintains blood sugar homeostasis. Gpr109A was activated by butyric acid, which combined with Gi protein to reduce intracellular cAMP, increase Treg production (FoxP3 expression), increase T cells producing IL-10, and reduce pro-inflammatory Th17 cells in lamina propria of the colon. Olfr558 has been proven to be activated by butyrate, which binds with Golf, Gs, and GS to affect prostate cancer. Olfr78 is expressed in blood vessels (smooth muscle cells) and renal afferent arterioles. Acetate and propionate, as ligands of Olfr78, regulate blood pressure by affecting renin release. (Lines of the same color represent the same path).

hexoses and pentoses, while deoxyribose and rhamnose are metabolized via the phosphate pathway.[96] Succinate is a precursor of propionate, and the succinate pathway is found mainly in many Negativicutes class and Bacteroidetes.[95] Some Bacteroidetes, notably *Prevotella copri*, and some *Ruminococcaceae*, such as *Ruminococcus flavefaciens*, produce succinate rather than propionate as an end product. However, some human colon bacteria are known to be Gram-negative bacteria belonging to the Firmicutes, for example, *Phascolarctobacterium succinatutens* can convert succinate to propionate; *Coprococcus catus* in the *Lachnospiraceae* has been shown to act via the acrylate pathway.[96]

Two acetyl coenzyme A molecules combine to form acetoacetyl coenzyme A, which is then progressively reduced to butyl coenzyme A, and then

further forms butyrate.[44] It is known that there are two different ways for the final step in the formation of butyrate from butyl coenzyme A, the butyl coenzyme A: acetate transferase pathway mediated by *Faecalibacterium prausnitzii*, which utilizes starch, hemicellulose, inulin, and pectin, and by *Eubacterium rectale*, which utilizes starch, arabinoxylan, and inulin[46] as well as mediated by the Firmicutes consisting of bacteria from *Roseburia*. The phosphotransbutylase and butyrate kinase pathways are mediated by colonies of some *Coprococcus* and *Clostridium species*.[96]

The intestinal epithelium absorbs most of the SCFAs produced in the colon. The liver transports and absorbs up to 50% propionate and 70% acetate produced by the intestinal tract, which is used to synthesize glucose, glutamine, glutamate, cholesterol, and ketone bodies, or used to produce ATP through β-oxidation, and only 5–10% SCFAs are excreted through feces. SCFAs can be eliminated by passive diffusion and by specialized transporter proteins (e.g., [MCT1/SLC16A1] and [SMCT1/SLC5A8]) into cells, which indirectly or directly affect the process of cell proliferation, differentiation, and gene expression.[44] It has been agreed that butyrate provides energy for colonocytes, but recently a different view has emerged. When butyrate is used as the source of ATP in colon cells, especially under the condition of glucose deficiency, the growth of cells is virtually inhibited by 10 mmol/l butyrate. Therefore, Fagundes et al. showed that butyrate is an important energy source for epithelial cells, but there must be other metabolites available for epithelial cell growth and repair.[44] SCFAs inhibit the proliferation of cancer cells and induce the death of apoptotic cells. SCFAs induce autophagy in colon cancer cell lines (HT-29, SW480, and HCT-116), which is a protective reaction against apoptosis. Butyrate promotes epithelial barrier function, while when it acts on intestinal stem/progenitor cells, it inhibits cell proliferation and delays wound repair via the transcription factor Foxp3.[97]

Intestinal microorganisms ferment SDF to produce propionate and butyrate to control body weight and blood glucose, possibly through complementary mechanisms that activate intestinal gluconeogenesis (IGN). IGN is beneficial to maintain glucose and energy homeostasis. Propionate, as a substrate of IGN, activates IGN gene expression through the gut-brain neural circuit involving GRP41. Butyrate activates the expression of the IGN gene via a cAMP-dependent mechanism.[98] Besides that, acetate can also inhibit appetite, which may be through the interaction with the central nervous system, butyrate and propionate induce the production of intestinal hormones that reduce food intake.[99] The abundance of *Parabacteroides* and *Fusicatenibacter* are related to higher fecal acetate and propionate, respectively, but only a very small fraction of SCFAs from the colon can reach the brain directly. On the contrary, downstream targets such as SCFAs inducing intestinal epithelial cells to release glucagonlike-peptide -1 (GLP-1) and peptide YY (PYY), and indirect signal transduction between vagus nerves or the regulation of liver metabolism, may be more important for intestinal-brain communication.[100]

3.2. DF increases the diversity of the BAs pool

BAs are amphiphilic cholesterol metabolites, the most important class of metabolites of the intestinal microbiota. BAs form micelles to solubilize dietary lipids in the small intestine and facilitate lipid absorption and excretion. Besides, they also play an important role in regulating immune signaling transduction, glucose and lipid homeostasis, and BAs biosynthesis.[101] The effect of DF on BAs is on the one hand to promote excretion through its physicochemical property, the encapsulation of secondary BAs,[102] on the other hand, it can increase the overall hydrophobicity and diversity of BA pool by changing the composition of the intestinal microflora, and the BA spectrum in the gut strongly depends on the type and amount of DF.[103]

In the molecular environment of the mammalian gut, BAs exemplify the synergistic metabolism of the host and its microbiota.[104] The first biological function of BAs is to remove cholesterol from the body. Cholic acid (CA) and chenodeoxycholic acid (CDCA) are primary BAs synthesized by cholesterol in the liver via either the cholesterol 7-α hydroxylase (CYP7A1)-mediated classical (neutral) pathway in hepatocytes or the cholesterol 27-hydroxylase (CYP27A1)-mediated alternative (acidic) pathway in extrahepatic tissues.[101]

The second function of BAs is that primary BAs are coupled with glycine (human) or taurine (mouse) to increase hydrophilicity, promote its transition to the bile duct cavity, and drive the flow of bile-salt-dependent bile. As a "cleaner", BAs emulsified dietary lipids in the process of intestinal digestion and absorption is its third classic function. Most of these BAs are reabsorbed by specific transporters at the end of the ileum and recycled to the liver. A small part of BAs is metabolized by intestinal microbiota into secondary BAs, which are passively reabsorbed and reach the liver to complete enterohepatic circulation.[105]

The action of intestinal bacteria on BAs is based, on the one hand, on the chemical transformation of primary BAs,[101] Primarily C24-amide hydrolysis and 7α-dehydroxylation convert the glycine and taurine couplings of CA and CDCA to secondary BAs: deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. DCA and LCA are the most abundant of about 50 different secondary BAs detected in human feces (Devlin & Fischbach, 2015). Hydrolysis of amino acids by bile salt hydrolase (BSH) is the first step of secondary BAs metabolism.[106] *Lactobacillus* is the most critical of the representative genera encoding BSH.[107] β-glucan significantly promoted the growth of *Lactobacillus*.[64] Bacteria further dehydroxylate and epimerize hydroxy groups on the steroid backbone of deconjugated BAs, The bai operon of bacteria is responsible for the dehydroxylation of BAs.[101] Fructooligosaccharides, pectin, and inulin-fed TLR5-deficient mice (T5KO mice) found that these soluble fibers could induce mice to suffer from cholestatic liver cancer. This was attributed to an imbalance in the intestinal microbiota as evidenced by a significant increase in the abundance of *Clostridium* cluster XIVa (e.g., *C. Hylemonae* and *C. Scindens*), which ferment the above-mentioned fibers and can convert primary BAs to secondary BAs by 7 α dehydration.[108] *C. hylemonae* and *C. scindens* generate 5β-reductase (5BR) based on the gene encoding of BaiCD, and 3-oxoΔ 4-DCA is transformed into 3-OxoDCA under the action of 5BR[109]; Additional bacterial modifications include desulfurization, esterification, oxidation/epimerization, and coupling (Collins, Stine, Bisanz, Okafor, & Patterson, 2022). Hydroxysteroid dehydrogenase (HSDH) is a key enzyme in oxidation/epimerization. 3αHSDH and 3βHSDH generated 3-oxoDCA from DCA for *Eggerthella lenta* and *Ruminococcus gnavus*, and played a key role in the process of 3-oxoDCA generating isoDCA.[104] Bacteria carrying 5α-reductase (5AR) and 3βHSDH-II at the same time, such as *Odoribacteraceae*, are necessary to produce ISOALLO-Lithocholic acid (ISOALLO-LCA) and related BAs.[110] The microbiota related to desulfurization includes *Proteobacterium, Fusobacterium*, *Peptococcus*, *Clostridium*, and *Pseudomonas spp*. *Bacteroides*, *Bifidobacterium*, *Enterococci*, and *Enterocloaster* are closely related to amide binding (Collins, Stine, Bisanz, Okafor, & Patterson, 2022). Supplementation with type 2 resistant starch reduces the abundance of *Peptococcus* in middle-aged and elderly mice reared on a high-fat diet.[111] Galactoglucomannan-rich hemicellulose extract significantly reduces Odoribacter abundance when fed to rats with prostatitis.[112] *Clostridium*, *Bacteroides*, *Bifidobacterium*, and *Lactobacillus* are the main glycolytic bacteria that metabolize DF in the human gastrointestinal tract.[113]

On the other hand, the microbiota regulates BAs metabolism and transport through several key host BAs receptors. Constitutive androstane receptor, Pregnane X receptor, Vitamin D receptor (VDR), and Farnesoid X receptor (FXR) serve as a bridge between BAs and nuclear receptor target genes involved in xenobiotic metabolism, glucose and lipid homeostasis, and immunomodulatory pathways, and several GPCRs also bind to BAs and have predominantly immunomodulatory functions.[101] CA, DCA, LCA, and CDCA, as natural ligands of FXR, can reduce inflammatory reactions and affect the progress of nonalcoholic steatohepatitis, liver cancer, gastrointestinal diseases, metabolic diseases, and other diseases through direct and indirect mechanisms[105]; $FXR^{-/-}$ causes the spontaneous formation of intrahepatic cholestasis in mice, *Lactobacillus gasseri* and *Lactobacillus johnsonii FI9785* were significantly reduced in the $FXR^{-/-}$ group.[114] TGR5 negatively regulates inflammation in a variety of pathological conditions, including type 2 diabetes, nonalcoholic steatohepatitis, liver disease, and atherosclerosis, and UDCA, CA,

CDCA, DCA, and LCA are its natural ligands.[105] [115] BAs act on RORg+ regulatory T cells via VDR to modulate adaptive immunity in mice, thereby reducing susceptibility to chemically induced colitis.[116]

However, impaired regulation of BAs adversely affects the organism, and serum total BAs levels are strongly correlated with Preterm birth (PTB), and BAs induce PTB in a dose-dependent manner, restoring BA homeostasis in vivo through activation of the FXR, which significantly reduces PTB and significantly increases neonatal survival rates.[117] *Bacteroides fragilis* inhibits FXR signaling through BSH activity, leading to excessive BAs synthesis and interruption of bile secretion in the liver eventually promoting intrahepatic cholestasis of pregnancy (ICP).[118] Supplementation with xanthan gum, arabinogalactan, xylan, apple pectin, arabinoxylan, β-glucan, glucomannan, carrageenan, and guar gum all reduced the abundance of *Bacteroides fragilis*.[64] Taurine deoxycholic acid (TCDCA) is toxic to primary mouse hepatocytes, inducing mitochondrial permeability transition (MPT) and Caspase-11 pyroptosis in mice. However, inulin increased the abundance of *Parabacteroides distasonis*,[71] which can increase BSH activity, inhibit FXR signal transduction, and decrease TCDCA level in the liver, which increases BAs excretion and improves liver fibrosis in mice.[119]

3.3. DF regulates tryptophan metabolism

As shown in Figure 2, Tryptophan (Trp) is metabolized mainly through three pathways directly or indirectly controlled by the microbiota, namely, the kynurenine (Kyn) pathway mediated by indoleamine 2,3- dioxygenase 1 (IDO1), indoleamine 2,3-dioxygenase 2 (IDO2), and tryptophan 2,3-dioxygenase 2 (TDO2), the indole derivative pathway, and the 5-hydroxytryptamine (5-HT) production pathway, in which tryptophan hydroxylase (TPH) is involved.[120]

Gut microbes directly convert Trp into indole and its derivatives. Many indole derivatives, such as indoleacrylic acid, indole-3-acetaldehyde (IAAld),

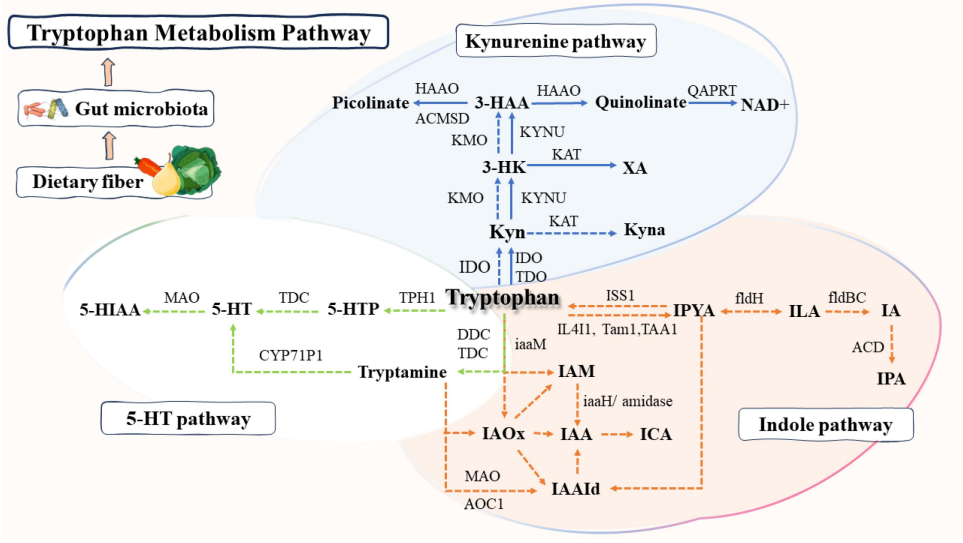

Figure 2. Tryptophan metabolism pathway. The solid line in the figure indicates the host pathway and the dashed line indicates the pathway involving the gut microbiota. Kyn: kynurenine; Kyna: kynurenate; 3-HK: 3-hydroxy-L-kynurenine; XA: xanthurenate; 3-HAA: 3-hydroxy-anthranilate; TDO: tryptophan 2,3-dioxygenase; IDO: indoleamine 2,3-dioxygenase; KAT: Kynurenine aminotransferase; KYNU: kynureninase; HAAO: 3-hydroxyanthranilate 3,4-dioxygenase; ACMSD: aminocarboxymuconate-semialdehyde decarboxylase; QAPRT: quinolinate phosphoribosyltransferase; 5-HTP: 5-Hydroxy-L-tryptophan; 5-HT: 5-Hydroxytryptamine (Serotonin); 5-HIAA: 5-Hydroxyindoleacetaldehyde; TPH1: tryptophan 5-monooxygenase; TDC: L-tryptophan decarboxylase; MAO: monoamine oxidase; CYP71P1: tryptamine 5-hydroxylase; IPYA: Indolepyruvate; ILA: Indole-3-lactic acid; IA: Indole acrylic acid; IPA: Indole-3-propionic acid; IAM: Indole-3-acetamide; IAA: Indole acetic acid; ICA: Indole-3-carboxaldehyde; IAAId: Indole-3-acetaldehyde; ISS1: aromatic amino-transferase; IL4I1: L-amino-acid oxidase; Tam1: tryptophan aminotransferase; TAA1: L-tryptophan – pyruvate aminotransferase; fldH: aromatic 2-oxoacid reductase; fldBC: phenyllactate dehydratase; ACD: acyl-CoA dehydrogenase; iaaM: tryptophan 2-monooxygenase; iaaH: indoleacetamide hydrolase; AOC1: diamine oxidase; MAO: monoamine oxidase

indole-3-propionic acid (IPA), indole-3-acid-acetic (IAA), and indole-3-aldehyde (IAld), are ligands for Aryl hydrocarbon receptor (AhR). AhR activation can downregulate inflammatory cytokines and upregulate IL-22, improve host immune homeostasis, and maintain intestinal barrier integrity.[121] [122] It can also inhibit the Wnt-β-catenin signal and limit the proliferation of intestinal stem cells by transcriptional regulation of Rnf43 and Znrf3, E3 ubiquitin ligase to prevent tumor occurrence.[123] The intestinal microorganism also affects the IDO pathway for the production of Kyn, and the microorganism involved in this process include *Ileibacterium valens*, *Parabacteroides distasonis*, *Shigella sonnei*, *Bacteroides acidifaciens*, *Bacteroides vulgatus* (taxonomic name change: *Phocaeicola vulgatus*) and *Burkholderiales bacterium YL45*, among other,[124] this pathway plays a key role in neurobiological functions, immune responses and inflammatory mechanisms.[120] In addition, *Burkholderiales bacterium YL45*, *Ileibacterium valens*, and *Parabacteroides distasonis* were significantly correlated with serum KATa and hepatic KAT2, suggesting that the gut microbiota may regulate serum kynurenic acid (Kyna) levels either directly or by influencing KAT2.[124] The ratio between the neuroprotective factor and neurotoxic factor affects normal brain function, and the metabolic mode of Kyn is different between these two nerve branches. In the neuroprotective branch, Kyn is converted into Kyna via kynurenine aminotransferase. Other metabolites are formed in neurotoxic branches, such as quinolinic acid (QA), xanthurenic acid (XA), anthranilic acid (AA), picolinic acid (PA), 3- hydroxy anthranilic acid (3-HAA), 3-hydroxykynurenine (3-HK). Overgrowth of intestinal bacteria will change Trp metabolism in the Kyn pathway, which may be the cause of emotional disorders and abdominal diseases.[125] In addition to this, peripheral serotonin production in enterochromaffin cells is also influenced by the intestinal microbiota, and it has been confirmed that some bacteria (e.g., Clostridial) have Trp decarboxylase, which converts Trp into neurotransmitter tryptamine. Tryptamine derived from microorganisms can be used as serotonin receptor 4 (also known as 5-HT4 receptor) expressed in the intestinal epithelium.[126] Gut-produced 5-HT has many local effects, such as regulating physiological processes such as cognition and reward, and the pathophysiology of depression is strongly associated with low levels of 5-HT.[127] 5-HT also stimulates gut motility, even though intestinal microflora does not cross the blood-brain barrier, it indirectly affects the central 5-HT pathway by regulating the availability of Trp and tryptamine.[120] *Parabacteroides* treatment affects tryptophan metabolism in the mouse hippocampus as evidenced by elevated 5-HT concentration and elevated 5-HT/Trp ratio.[127]

DF affects tryptophan metabolism by influencing the intestinal microbiota. This is partly because DF delays or reduces the absorption of a large number of nutrients in the small intestine, resulting in more dietary tryptophan not being fully absorbed and entering the large intestine to be metabolized by the gut microbiota. Second, higher DF may downregulate or inhibit tryptophan metabolism toward the kynurenine pathway, leading to a greater shift in tryptophan metabolism toward the indole derivative pathway.[128] Finally, other substances produced by fermenting DF (e.g., SCFAs) may help shape the gut microbial community by influencing bacterial cross-feeding to be more favorable for species that metabolize Trp to colonize.[129] For example, in an experiment of butyrate intervention in mice with rheumatoid arthritis, it was found that butyrate supplementation inhibited arthritis in a Breg-dependent and microbe-independent manner (butyrate supplementation was ineffective in inhibiting arthritis in quadruple antibiotic-treated mice) by increasing the levels of the serotonin-derived metabolite, 5-hydroxyindole-3-acetic acid (5-HIAA), which activates AhR, and that supplementation of Mice supplemented with butyrate had increased numbers of the bacterial genera *Allobaculum*, *Bifidobacterium*, and *Rhodosprillaceae_unclassified*, which are implicated in Trp metabolism, compared to controls.[130]

Supplementation of healthy rats with arabinogalactan, β-glucan, and glucomannan increased tryptophan metabolism, especially ILA levels were significantly elevated by β-glucan intervention, while treatment with arabinoxylan, carrageenan, and guar gum showed the opposite trend. This may be because DF selectively increased the abundance of *Lactobacillus*, *Bacteroides*, *Butyricimonas*, *Treponema*, *Prevotella*, and *Phascolarctobacterium*

and decreased the abundance of *Bacteroides fragilis* and *Clostridium perfringens*. Among them, *Lactobacillus*, *Bacteroides*, *Clostridium*, and *Desulfovibrio* were significantly related to tryptophan metabolism. *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, and some other bacteria of *Bacteroide* have been shown to produce Kyn, IAA, and indole-3-lactic acid.[64] IPA production has been shown to be entirely dependent on the gut microbiota and is particularly associated with *Clostridium*, e.g., *Clostridium sporogenes*, *Clostridium cadaveris*.[131]

4. Prebiotic-like physiological roles of DF

4.1. DF reduces the risk of cardiovascular disease (CVD)

CVD is a worldwide common cause of death.[132] DF intake can reduce CVD mortality, cancer mortality, and all-cause mortality.[133] There is considerable epidemiological evidence that DF intake is negatively correlated with the risk of CVD. People have long known that regular consumption of dietary fiber, especially fiber from grains, can improve CVD through various mechanisms,[134] including reducing lipids, regulating body weight,[135] improving glucose metabolism,[136] controlling blood pressure[137] and reducing chronic inflammation.[138]

4.1.1. DF affects atherosclerosis by regulating trp metabolism

Atherosclerotic cardiovascular disease (ASCVD) is characterized by narrowing or blockage of arteries and is a major risk factor for CVD.[87] As shown in Figure 3, Low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apolipoprotein (Apo)B lipoproteins remain in the arterial wall, which is the key initial event of atherosclerosis. The LDL-C value is positively correlated with the risk of cardiovascular events in the future to some extent.[139] Supplementation with specific DF can indirectly provide health benefits by increasing the abundance of the bacteria associated with Trp metabolism. For example, the representative strains of the human gut: *Lactobacillus plantarum*, *Bacteroides dorei*, *Bifidobacterium adolescentis Clostridium symbiosum*, and *Escherichia coli* were cultured individually/combined in media with xylan or inulin as carbon source, and it was found that the bacteria in inulin grew faster and *B. adolescentis* and *L. plantarum* were the dominant groups, while *B. dorei* and *C. symbiosum* were the dominant groups in xylan.[140] The positive effects of bacteria such as *Lactobacillus* and *Bacteroides* on tryptophan metabolism have been stated in 3.3. Intestinal microorganisms metabolize tryptophan to produce indole-3-carboxaldehyde (ICA) and indole-3-propionic acid (IPA), which can inhibit the progress of ASCVD and alleviate the phenotype related to atherosclerosis. Measurement of plasma tryptophan metabolites in healthy individuals and patients with atherosclerosis revealed lower ICA concentrations in the patient group, but no significant differences in tryptophan levels. Similarly, the high-fat diet (HFD) experimental mouse group showed a consistent pattern of data with clinical presentation and lower abundance of Bacteroidaceae and Lactobacillaceae in the HFD group than in the control group, whereas these bacteria have been shown to produce tryptophanase, which metabolizes tryptophan to ICA. The lack of these gut microorganisms prevented the metabolism of tryptophan to ICA. The total plaque area in the entire aorta was reduced by 40% after ICA treatment was given to mice in the HFD group. ICA alleviates atherosclerosis-associated phenotypes by triggering the Nrf2-HO-1 pathway in endothelial cells through activation of the AhR, which increases the transcriptional level of endothelial nitric oxide synthase (eNOS), and decreases the gene expression of vascular cell adhesion molecule (VCAM), C – C motif chemokine ligand 2(CCL2), and interleukin- 6, as well as the level of reactive oxygen species (ROS). After AhR knockdown, ICA no longer controls the expression of the above factors in relation to each other. Knockdown of NF-E2-related Factor (Nrf2), a target of AhR binding to ICA, revealed a decrease in the expression of heme oxygenase (HO-1) and AhR, but an increase in the expression of CCL2 and IL6. On the basis of the knockdown of Nrf2, endothelial cells did not increase eNOS expression and did not decrease VCAM and ROS expression, even when treated with ICA.[141]

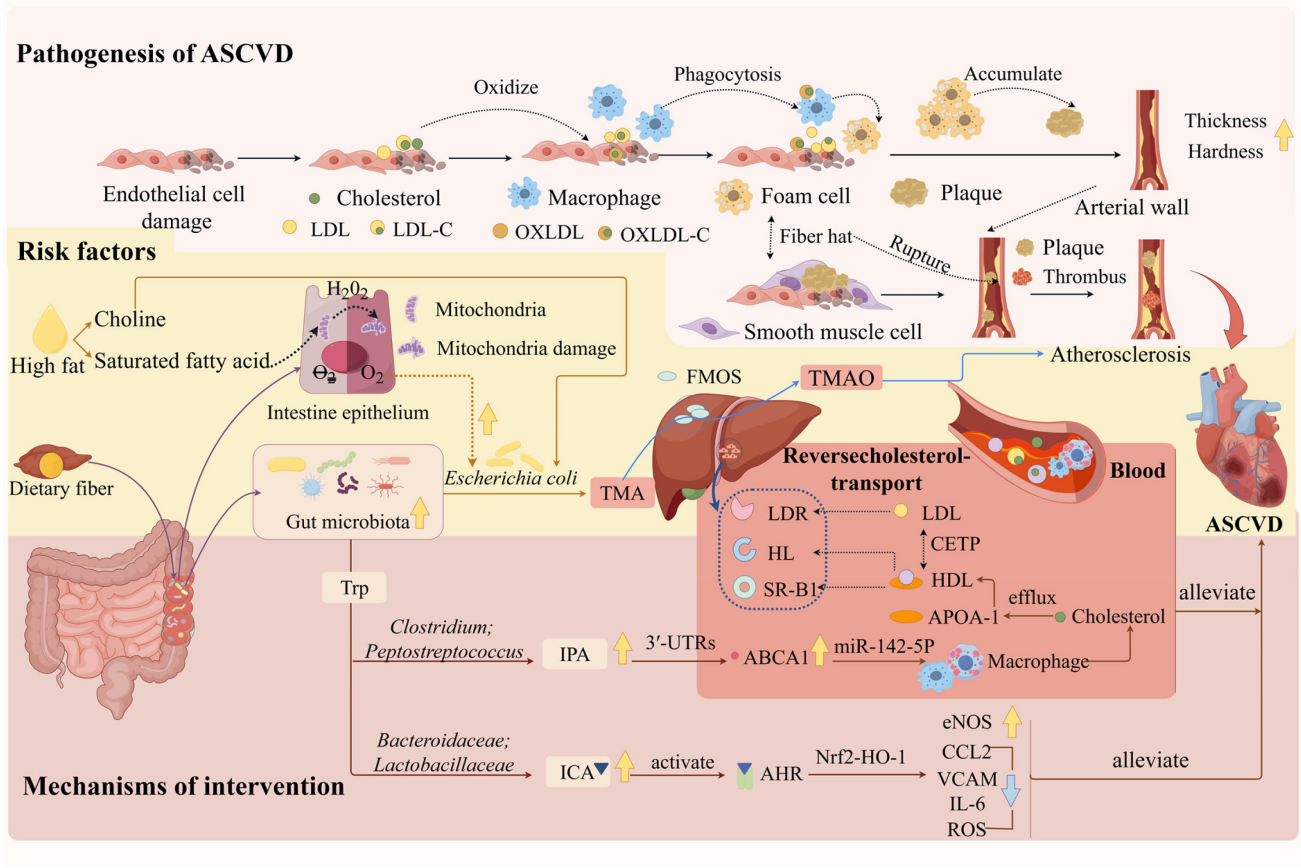

Figure 3. Mechanisms of ASCVD and their relationship to DF and gut microbiota. Damage to the endothelial cells lining the arteries causes substances such as cholesterol, fats, and cellular metabolites from the blood to accumulate in the damaged area. During the accumulation of substances, oxidation of LDL-C causes an inflammatory response in endothelial cells, and monocytes in the blood receive inflammatory signals to move toward the damaged area. Stimulated by OXLDL-C, monocytes transform into macrophages, which ingest and digest cholesterol molecules to become foam-like cells. Foam-like cells accumulate to form plaque, and with the accumulation of plaque, the arterial wall hardens and thickens. Meanwhile, the smooth muscle cells in the inner wall of the artery begin to proliferate, and most of the smooth muscle cells move to the surface of the plaque, forming a hard fibrous cap covering the plaque. As a result, the diameter of the arterial vessels becomes narrowed, blood flow is reduced, and atherosclerosis develops. The fibrous cap eventually corrodes and ruptures, releasing the plaque into the bloodstream. The plaque forms a thrombus with the blood flow, blocking the blood flow and ultimately causing insufficient blood supply to the tissues around the blocked blood vessel site, which leads to ischemic necrosis of the surrounding tissues. In the colon, the high consumption of oxygen by mitochondria can maintain the anoxic state of epithelial cells, and then inhibit the overproduction of facultative anaerobic bacteria (such as *Enterobacteriaceae*). However, long-term consumption of a high-fat diet rich in saturated fatty acids will induce mitochondria to produce hydrogen peroxide (H_2O_2), which will destroy the bioenergy of mitochondria in colon epithelial cells. The increase of oxygen (O_2) provides a certain survival advantage for aerobic respiration of *Escherichia coli*. Promote *Escherichia coli* to further metabolize choline into TMA, which enters the liver and is further converted into toxic metabolite TMAO by FMOs, which enters the blood circulation and increases the risk of CVD. DF metabolizes tryptophan to produce the indole product ICA, which activates the Nrf2-HO-1 pathway by triggering AhR, thus reducing the levels of pro-atherosclerotic factors and ROS. IPA affects the normal functioning of the miR-142-5p/ABCA1 signaling pathway and inhibits atherosclerosis by promoting reverse cholesterol transport. LDL: Low-density lipoprotein; LDL-C: Low-density lipoprotein cholesterol; OXLDL-C: Oxidized Low-density Lipoprotein cholesterol; ASCVD: Atherosclerotic cardiovascular disease; TMA: trimethylamine; TMAO: trimethylamine oxide; FMOs: flavin monooxygenase; Trp: tryptophan; IPA: indole-3-propionic acid; ICA: indole-3-carboxaldehyde; 3′UTRs: 3′ untranslated regions; ABCA1: ATP-binding cassette transporter A1; LDR: LDL Receptor; HL: Hepatic Lipase; SR-B1: Scavenger Receptor-B1; APOA-I: apolipoprotein A-I; HDL: High-density lipoprotein; CETP: cholesterolestertransferprotein; AHR: aromatic hydrocarbon receptor; eNOS: endothelial nitric oxide synthase; VCAM: vascular cell adhesion molecule; CCL2: C – C motif chemokine ligand 2; ROS: reactive oxygen species; IL-6: interleukin 6.

Tryptophan metabolism is lower in the gut microbiome of CAD patients compared to healthy control subjects, while IPA shows the most significant decrease. Simultaneously, the presence and abundance of the phenylacetate dehydratase (fldBC) gene cluster was reduced, and the major IPA-producing bacteria (Clostridium and Peptostreptococcus, which correlated significantly

with serum IPA levels) were depleted. Similarly, there was a significant negative correlation between atherosclerotic lesion area and serum IPA levels in ApoE$^{-/-}$ mice.[142] Physiologically accessible concentrations of IPA (0.25–1 μmol/L) dose-dependently reduced lipid accumulation in acetylated low-density lipoprotein (AcLDL)-loaded macrophages and promoted cholesterol efflux from AcLDL-loaded macrophages to apolipoprotein A-I (ApoA-I) to attenuate AcLDL-induced macrophage foam cell formation. Specifically, IPA supplementation increased the expression of ATP-binding cassette transporter A1 (ABCA1) protein, a key transporter of macrophage RCT, in diseased macrophages.ABCA1 stimulated cholesterol efflux to ApoA-I. IPA enhances ABCA1 mRNA stability and extends the half-life of ABCA1 mRNA through the sequence of 3'untranslated regions (3′-UTRs) of ABCA1, thereby post-transcriptionally regulating ABCA1. The mouse or human ABCA1 3′-UTRs have 2 or 1 putative miR-142-5p binding sites, respectively, and miR-142-5p dose-dependently reduces mouse and human ABCA1 3′-UTR activity.[142] The abnormal expression of miR-142-5p caused by the decrease of IPA affects the normal operation of the miR-142-5p/ABCA1 signal pathway, reducing the outflow of cholesterol from macrophages and accelerating the progress of atherosclerosis. Dietary administration of IPA or intravenous miR-142-5p antagonists can mitigate or even reverse atherosclerotic plaque development by promoting macrophage reversal of cholesterol transport. According to this pathway, IPA may be a potential intervention target for microbial metabolism treatment of ASCVD.[142]

4.1.2. DF is fermented to produce SCFAs to regulate hypertension

Starting from 115/75 mmHg, the risk of CVD will be doubled with each increase of 20/10 mmHg.[143] Experimental and clinical evidence shows that the change in intestinal microbiota is related to and may cause a change in blood pressure.[144] Systems involved in blood pressure regulation, including the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), endothelium, natriuretic peptides, and the immune system.

Immune system activation and function play a key role in mediating the effects of microbiota on hypertension, and several immune cell types that promote or regulate hypertension are directly affected by changes in microbiota or microbe-dependent signaling pathways.[145] For example, in mice and humans, high salt treatment resulted in increased blood pressure and decreased abundance of *Lactobacillus spp*. [146] Moderate salt reduction in untreated hypertensive patients lowers blood pressure and improves arterial compliance, and clinical outcomes were accompanied by the increase of SCFAs in 8 kinds of circulation, except acetate, isovalerate, and propionate, where statistically significant increases were observed for 2-methylbutyrate, butyrate, hexanoate, isobutyrate, and valerate.[59] [147] This may be because the salt leads to the accumulation of isolevuglandins (IsoLGs, a toxic lipid byproduct) in dendritic cells, which leads to the activation of T cells and the production of pro-inflammatory cytokines such as Tumor necrosis factor (TNF), Interferon γ (IFNγ) and Interleukin 17(IL-17).[145] SCFAs can delay inflammation and fibrosis by reducing helper T cell 17 (TH 17) cells, increasing Treg cells, and reducing the IL-17, IFNγ, and IL-1 β.

Treatment with either high-resistant starch or butyrate, acetate, and propionate, respectively, reduced hypertension in angiotensin II (Ang II) – stimulated mice, with acetate having the most dramatic effect. Compared with low-resistant starch, high-resistant starch-treated hypertensive mice had lower mRNA expression of B-type natriuretic peptide (Nppb, which is a marker of cardiac hypertrophy and heart failure) and connective tissue growth factor (Ctgf), which were more similar to healthy cardiovascular parameters and markers. One of the possible mechanisms is through the regulation of the blood pressure-lowering catecholamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA).[148] Although the significance of the increase in L-DOPA levels by SCFAs is unclear, similarly, the addition of SCFAs to a diet of low-resistant starch increased plasma L-DOPA levels. In addition, mice without Ang II stimulation that knocked out the most common receptors for SCFAs signaling (GPR41, GPR43, and GPR109A) had enhanced fibrosis, cardiac hypertrophy, and end-diastolic pressure, suggesting that these receptors may play an important role in regulating cardiovascular

homeostasis.[148] Gpr41 is expressed in the autonomic ganglia and vascular endothelium, and its activation promotes ERK1/2 phosphorylation to regulate blood pressure.[149] Gpr109A is expressed in the rostral ventrolateral medulla (RVLM), where it responds to the activation of nicotinic acid as a nicotinic acid receptor to control blood pressure and lead to the increase of L- glutamate and ROS production.[149] Acetate and propionate, as ligands of Olfr78, activate the expression of Olfr78 in renal afferent arterioles and blood vessels (smooth muscle cells), where it has been shown to regulate blood pressure by affecting renin release.[149]

Besides, SCFAs inhibit the renin-angiotensin-aldosterone system (RAAS) and activate the vagus nerve to reduce the sympathetic nervous system to achieve the purpose of regulating blood pressure.[145] Hypertensive mice in the deoxycorticosterone acetate (DOCA)-salt model treated with high fiber (72.7% fiber) and acetate, respectively, had altered cardiac and renal transcriptomes compared with mice fed a control diet (47.6% fiber). In the kidney, renin-angiotensin system protein activator-like 1 (Rasal1, associated with renal fibrosis), cytochrome P450 family 4 subfamily α polypeptide 14 (Cyp4a14, which regulates the absorption of sodium via sodium channel fluid) and cholecystokinin (Cck, which has anti-inflammatory effects) were among the 244 genes co-expressed in high fiber and acetate. Second, fiber and acetate downregulated mRNA for early growth response protein 1 (Egr1, a major regulator of cardiac and renal fibrosis, inflammation, and cardiac hypertrophy) in the kidneys and heart, upregulated the regulation of circadian rhythms and downregulated the RAAS system in the kidneys and mitogen-activated protein kinase signaling in the kidney and heart.[150]

Ruminococcus bromii, *Faecalibacterium prausnitzii*, *Eubacterium hallii*, *Eubacterium rectale*, and *Bifidobacterium adolescentis* usually colonize the large intestine and have enzymes that digest DF for the production of SCFAs.[59] However, not all sources of DF can control hypertension. For example, a high intake of β -glucan fiber corresponds to a lower level of hypertension, while diets rich in mannan and xylan had no significant correlation with hypertension.[151] Cereal fiber has been shown in studies to reduce the incidence of inflammation-mediated CVD.[152] In contrast, there was no significant correlation between IDF from refined grain and new-onset hypertension.[153] This may be related to the different preferences of the intestinal microorganisms for DF.

4.2. DF affects liver disease by regulating the BAs pool

Consuming more DF reduces the incidence of liver cancer and liver disease mortality.[154] Alcoholic liver disease (ALD), as a chronic liver disease, is widely prevalent in the world.[155] Transplantation of feces from alcohol-fed anti-ALD mice or treatment of alcohol-induced ALD with pectin significantly reduces the severity of liver lesions in mice and even reverses liver injury.[156] This is because sensitivity to ALD in alcohol-fed mice is driven by the intestinal microorganism. Dysregulation of the intestinal microorganism profile leads to altered levels of BAs, which not only induce metabolic disorders, liver inflammation, oxidative stress, and fibrosis but even leads to liver cancer.[157] The relationship between hepatic lipid metabolism and gut microbiota is shown in Figure 4.

Gut microbiota imbalance promotes hepatocarcinogenesis via the tryptophan metabolism-AhR-SREBP2 axis between the liver and gut, and the AhR agonist Ficz inhibits post-translational expression of sterol regulatory element-binding protein 2 (SREBP2) and reverses hepatic tumorigenesis in mice, whereas tumorigenesis is accelerated in AhR knockout mice. Supplementing *Lactobacillus reuteri* can inhibit the expression of SREBP2 and tumorigenesis in mice with intestinal microorganism imbalance.[158] In addition, *Lactobacillus reuteri* inhibited lipopolysaccharide (LPS)-induced down-regulation of BAs metabolism-related molecule CYP7A1 and up-regulation of Retinoic acid receptor-related orphan receptor γ (RORγ), decreased total BAs and deoxycholic acid, and increased the level of ursodeoxycholic acid (UDCA), which inhibited JNK signaling to alleviate TNF-α-mediated apoptosis and ameliorate the LPS-induced hepatic injury in mice.[159] Similarly, the abundance of *Bacteroides thetaiotaomicron* was reduced in ALD mice, whereas supplementation maintained its abundance, ameliorated hepatic steatosis, and lowered triglyceride levels. On the one hand, this is because *B. thetaiotaomicron*

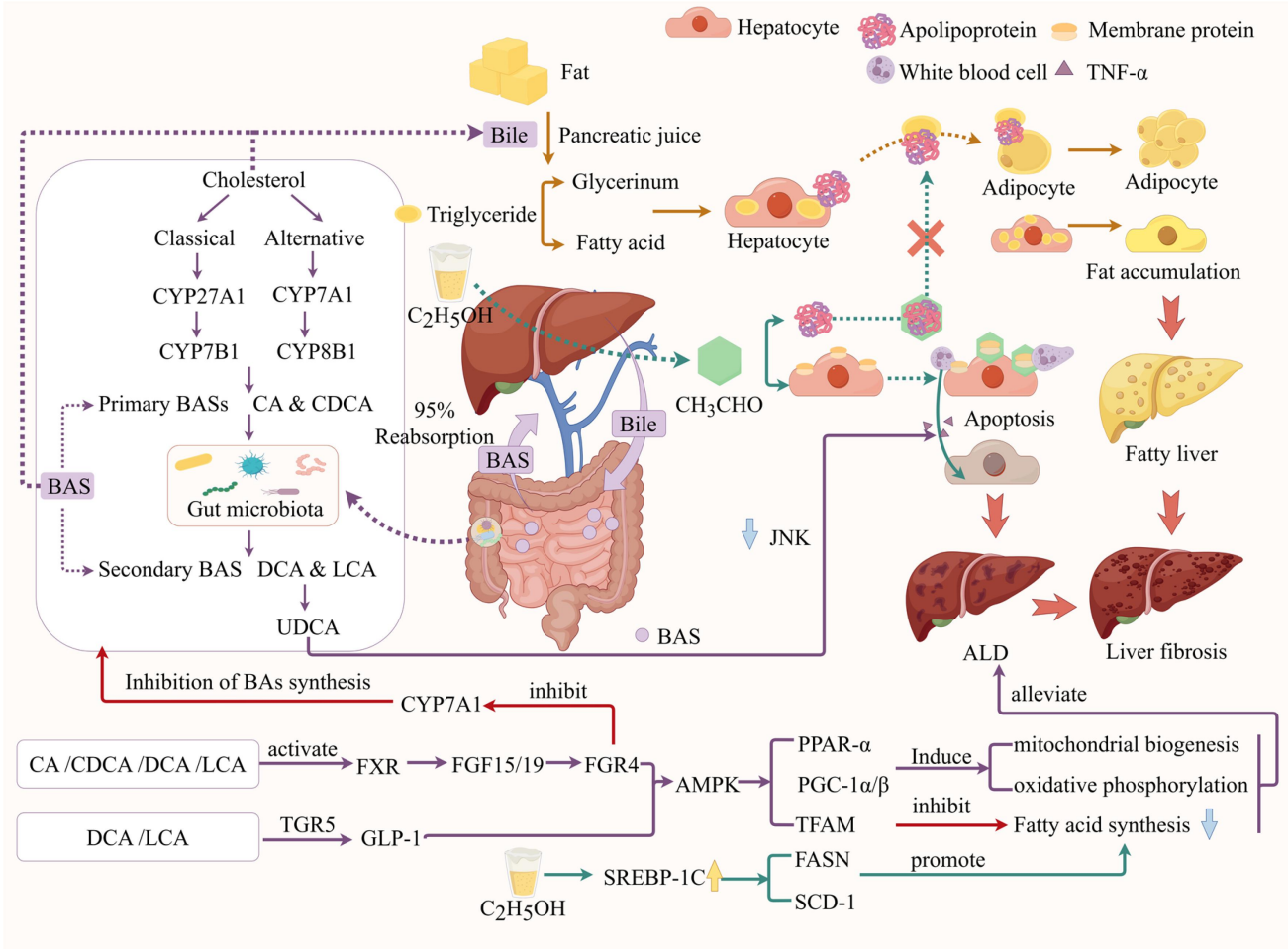

Figure 4. Liver lipid metabolism. Dietary fat is broken down by bile and pancreatic juice into glycerol and fatty acids, which synthesize triglycerides, which combine with apolipoproteins, phospholipids, and cholesterol to form very-low-density lipoproteins that are then secreted into the bloodstream by hepatocytes and transported to extra-hepatic tissues (adipocyte storage). Acetaldehyde, a product of ethanol metabolism, is hepatotoxic. Acetaldehyde binds to proteins to form acetaldehyde adducts that interfere with normal lipid metabolism in the liver. Acetaldehyde binds to apolipoproteins to form acetaldehyde adducts that impede fat transport, and fat accumulates in hepatocytes, forming alcoholic fatty liver; Acetaldehyde binds to membrane proteins on hepatocytes, triggering an immune response and alcoholic hepatitis. Massive hepatocyte injury and death induce self-fibrous tissue repair further leading to liver fibrosis. Bile contains phospholipids, cholesterol, and other substances, of which BAs combined with sodium and potassium to form BA salts occupy 50% of the bile. In the liver, cholesterol is the raw material for the formation of primary BAs via the classical and alternative pathways. Normally, over 75% of BAs is synthesized by the classical pathway, cholesterol is catalyzed by the rate-limiting enzyme CYP7A1 to form 7-hydroxycholesterol, which is further catalyzed to form CA and CDCA. In the alternative pathway, cholesterol undergoes C27 hydroxylation catalyzed by the CYP27A1, followed by 7-hydroxylation catalyzed by the CYP7B1, which produces predominantly CDCA. Glycine and taurine couplings of CA and CDCA can be converted by gut microbiota to secondary BAs: DCA and LCA, respectively. About 95% of BAs can be reabsorbed by the gut. Reabsorbed BAs reenter the liver via the portal vein, where free BAs are reconverted to bound BAs in the hepatocytes, and together with the reabsorbed and newly synthesized bound BAs, they enter the intestine along with the bile to complete the hepatic-intestinal cycle. UDCA, a secondary BA, inhibits JNK signaling, attenuates TNF-α-mediated hepatocyte apoptosis, and ameliorates liver injury. BAs: bile acids; CYP27A1: cholesterol 27-hydroxylase; CYP7A1: cholesterol 7-α hydroxylase; CYP7B1: oxysterol 7-alpha-hydroxylase; CYP8B1: cytochrome P450 8B1; CA: cholic acid; CDCA: chenodeoxycholic acid; DCA: deoxycholic acid; LCA: lithocholic acid; UDCA: ursodeoxycholic acid; ALD: Alcoholic liver disease; TNF-α: Tumor Necrosis Factor Alpha; PPAR-α: Peroxisome Proliferator Activated Receptorα; PGC-1α/β, peroxisome proliferator-activated receptor-gamma coactivator-1α/β; TFAM: Transcription Factor A, mitochondrial; FGFR4: Fibroblast Growth Factor Receptor 4; AMPK: 5′ AMP-activated protein kinase; SREBP-1c, Sterol-regulatory element-binding protein-1C; FASN: Fatty acid synthase; SCD-1: Stearoyl-CoA desaturase; FGF15: fibroblast growth factor 15; GLP-1: Glucagon-like peptide-1;

restores the intestinal mucosal barrier function and reduces LPS production by increasing mucus thickness, promoting mucin2 production, and inhibiting phosphorylation of matrix metallopeptidase 9 (MMP9), extracellular signal-regulated kinase 1/2 (ERK), and Notch signaling.[66] On the other hand, as described in Section 3.3, CA, CDCA, DCA, and LCA, as well as taurine or glycine couplers were identified as endogenous agonists of FXR that activate FXR,[105] which in turn promotes transcription of Fibroblast Growth Factor 15/19 (FGF15/19). FGF15/19 binds in the liver to Fibroblast Growth Factor Receptor 4 (FGFR4) in the liver and inhibits CYP7A1 and BAs synthesis. Glucagon-like peptide-1 (GLP-1) is an enteroglucagon, and GLP-1 expression in the colon can be mediated by Takeda G protein-coupled receptor 5 (TGR5) regulated by BAs (DCA and LCA).[115] 5' AMP-activated protein kinase (AMPK) serves as a target of FGFR4 and GLP1R signaling, which targets Peroxisome Proliferator-Activated Receptorα (PPAR-α), Peroxisome Proliferator-activated Receptor-gamma coactivator-1α/β (PGC-1α/β) and Mitochondrial Transcription Factor A (TFAM), whose main functions are to induce mitochondrial biogenesis, oxidative phosphorylation (OXPHOS), inhibit fatty acids (FA) synthesis and stimulate fatty acids (FAO).[66] Sterol-regulatory element-binding protein-1C (SREBP-1c) is a known transcription factor involved in FA synthesis genes such as Fatty acid synthase (FASN) and SCD-1 (Stearoyl-CoA desaturase). Alcohol stimulates FA synthesis by affecting the production of FGF-15 and GLP-1, inhibiting AMPK and enhancing SREBP-1c.[66] *B. thetaiotaomicron* up-regulates GLP-1 and down-regulates FGF15, thereby regulating BAs metabolism. *B. thetaiotaomicron* also restores phosphorylation of AMPK, decreases SREBP-1c levels, and inhibits fatty acid synthesis, as well as improves mitochondrial adaptations and functions, and ultimately improves lipid metabolism in the liver.[66]

Pectins are plant cell wall polysaccharides rich in d-galacturonic acid (d-GalA), and the two main types of pectins are rhamnogalacturonan I (RGI) and homogalacturonan (HG). Harry J. Gilbert et al. made a detailed study on the polysaccharide degradation system of *B. thetaiotaomicron* and other Bacteroides degrading HG and RGI[160]; In addition to this, another common polysaccharide in pectin, rhamnogalacturonan II (RG-II), and *B. thetaiotaomicron* was able to utilize the large number of CAZymes contained in the three polysaccharide utilization loci (PUL) to degrade RG- II almost completely (leaving an uncracked glycosidic bond).[2] This may explain why pectin treatment improves disease outcomes in ALD.[161] Whereas the CAZymes of *Lactobacillus reuteri* are mainly composed of GHs and GTs, PLs and AAs are absent, and supplementation with appropriate amounts of oligosaccharides can be used as a preferred substrate for the growth of *Lactobacillus reuteri*.[162]

However, the results of DF interventions in disease are not always positive. Feeding guar gum to nonalcoholic fatty liver disease (NAFLD) mice, while reducing inflammation and the lump of adipose tissue, nevertheless also augmented inflammation and fibrosis of the liver, while significantly elevating hepatic and plasma BAs levels. Compared with guar gum, long-term oral antibiotics effectively inhibited intestinal bacteria, (22 consecutive weeks of oral ampicillin, neomycin sulfate, metronidazole, and vancomycin, an antibiotic mixture that has been proved to destroy all detectable commensal bacteria), reduced the level of secondary BAs in portal, and liver inflammation and fibrosis are alleviated.[163] Therefore, a lot of research is needed on how to balance the relationship between DF intake and the gut microbiota as well as disease.

4.3. DF affects immunity by regulating trp metabolites, SCFAs, and BAs

β-glucan is a natural cell wall polysaccharide derived from grains and microorganisms that promote healthy skin,[164] which may benefit from gut microbiota. Microorganisms play a key role in immunology, metabolism, and endocrine through indirect or direct communication in the gut-skin axis, and oral probiotics or control of the microbiota itself may help treat atopic dermatitis (AD).[165] A combination of β-glucan extracted from oats with probiotics can improve the pathological changes in AD mice.[166] Treatment of 1-chloro-2,4 dinitrobenzene (DNCB)-induced AD mice with a mixture of long-chain fructooligosaccharides and short-chain galactose oligosaccharides, β-glucan, or inulin revealed that

the disease remission benefited from the above DF to improve Th1/Th2 cytokine homeostasis and the levels of beneficial commensal microbes.[167]

In addition to affecting the gut-skin axis, DF also exerts an inhibitory effect on other allergic reactions. FOS can protect mice from food allergy (FA) induced by ovalbumin (OVA), significantly reduce the levels of ROR-γt and IL-17A, and increase the levels of Forkhead box protein P3 (Foxp3) and IL-10 in FOS mice.[168] Previously, we have known that IL-17 is secreted by helper T cells17 and transcription is mediated by ROR-γt to cause inflammation in the body.[169] Whereas Treg cells can suppress T cell responses and are involved in blocking autoimmunity, Foxp3 plays a key role in Treg cell differentiation and function,[170] one of the main characteristics of Foxp3+ Treg cells is that they constitutive high express CD25 (IL-2 receptor α chain), which forms a high-affinity interleukin-2 (IL-2) receptor and a co-inhibitory molecule CTLA-4 together with β chain and γ chain. Foxp3 + Treg cells can also make extensive use of other inhibitory molecules to achieve immunosuppression, including TGF-β, IL-10, and so on.[171] In addition to this, FOS reversed the elevated fecal abundance of Akkermansiaceae and Verrucomicrobia, as well as the decreased abundance of Ruminococcaceae in the feces of the OVA-allergic mice; the analysis of Trp metabolites showed that serum Kyn levels were significantly decreased in OVA mice, while the levels of 5-HT and Trp increased significantly, although the above-mentioned changes had no impact on the aromatic hydrocarbon receptor-antagonist (AhR-A) mice.[168] Inflammatory tissues are mainly involved in three kinds of Trp metabolism pathways: Trp depends on the IDO1 is metabolized into Kyn in immune cells and epithelial cells, 5-HT is produced in enterochromaffin cells by Trp hydroxylase 1, and Trp is converted into indole and indole derivatives as endogenous physiological AhR agonists by specific intestinal flora.[126] Among them, IDO1-mediated Kyn pathway accounts for about 95% of Trp degradation as negative feedback regulation of inflammatory reaction, and the expressions of IDO1 and AhR can be enhanced by AhR itself, thus forming IDO1-AhR self-amplification loop for effective suppression of the immune response.[172] FOS can improve the allergic symptoms of mice by regulating the composition of intestinal flora and the balance of Th17/Treg by Trp metabolites.[168]

In addition to the Trp pathway regulating immune function, intestinal flora metabolism DF can also increase the concentration of circulating SCFAs to shape the immune environment and affect the severity of allergic inflammation. SCFAs, as ligands of G protein-coupled receptors (GPCRs), include GPR41, GPR43, and GPR109A, thus activating the anti-inflammatory signal cascade.[97] Furthermore, butyrate and propionate influence the differentiation and function of dendritic cells, macrophages, and T cells. Rather than acting as energetic substrates or signaling through GPCR, these SCFAs act as histone deacetylase inhibitors, directly affecting the intrinsic function of B cells by inhibiting the expression of Activation-induced cytidine deaminase (AID) and Blimp1(B lymphocyte-induced maturation protein 1), which results in the up-regulation of specific miRNAs targeting Aicda- and Prdm1-3 'UTRs to upregulate specific miRNAs.[173] Prdm1 (PR domain zinc finger protein 1)/Blimp1 regulates the differentiation of T cells and B cells and plays a key role in T-cell-mediated immunosuppression.[174 175]

While innate immunity helps to clear pathogens, over-activation of innate immunity leads to a cytokine storm that may result in exacerbation of pathologic development. Innate immune cells express germline-encoded pattern-recognition receptors to monitor the release of pathogen-associated molecular patterns (PAMPs) by microorganisms or the release of damaged cell-danger-associated molecular patterns (DAMPs) released by microorganisms or by damaged cells.[176] Mitochondria determine cell metabolism and fate and are the central hub for the regulation of innate immune responses to PAMP and DAMP. BAs (DCA and CDCA) are a class of DAMP-activated NLRP3 inflammasome and under conditions of cholestasis, high concentrations of BAs activate endogenous mitofusin 2 (MFN2) and promote mitochondrial endoplasmic reticulum tethering, leading to calcium transfer from the endoplasmic reticulum to mitochondria, which activates NLRP3 inflammasome and pyroptosis.[176] In addition, BAs may trigger mitochondrial permeability shifts and promote Apaf-1/caspase-4 pyroptosome- and

gasdermin E (GSDME)-dependent pyroptosis.[177] In contrast, at physiologically relevant low concentrations, BAs promote mitochondrial fusion, leading to enhanced oxidative phosphorylation and thus enhanced phagocytic clearance of bacteria mediated by infiltrating macrophages.[176]

5. DF and precision nutrition

The body's gut microbiota varies greatly, with the elusive configuration of a healthy microbiome. The definition of the microbiome is a catalog of all microorganisms and their genes in a place, encoding more than 40 million different gene variants. Half of these gene variants are unique to a single individual.[59] The remarkable heterogeneity of human microbiome data depended to a great extent on different dietary habits. The fecal microbiota of Burkina Faso children from Africa with a diet rich in resistant starch and fiber was significantly enriched in Bacteroidetes and significantly reduced in Firmicutes ($p < 0.001$), with the distinctive bacterial abundance of *Prevotella* and *Xylanibacter*, whereas in the Western diet similar to that of Western children and low in fiber European children were completely lacking.[178] In contrast, DF selectively affects the gut microbiota, producing different effects on different diseases. Inulin intervention has been proven to effectively reduce the expression of HDAC9 in asthma patients, decrease airway eosinophils, and improve asthma control. At the same time, however, inulin altered microbial metabolism in mice, leading to increased levels of BAs throughout the body, which triggered an increase in stromal cell-derived IL-33 and subsequent activation of ILC2s to produce IL-5, leading to tissue eosinophilia and type 2 inflammation. However, if bacteria lacking BAs metabolizing enzyme genes are used, the effect of type 2 inflammation caused by inulin will be eliminated.[179] Therefore, no generalizations can be made when using DF in response to disease, and the heterogeneity of the background of the human intestinal microbiota is critical to the impact of disease. What kind of dietary environment leads to what kind of microbiota background is also a subject for further research.

Differences in the composition of DF trigger specific responses in the intestinal microbiota. carrageenan intervention increased the abundance of *Treponema*, *Prevotella*, and *Phascolarctobacterium*. Xylan treatment increased the abundance of *Paraprevotella*, *Desulfovibrio, Dehalobacterium*, and *Butyricimonas*. Supplementation with Glucomannan treatment significantly increased the abundance of *Ruminococcus*, arabinogalactan increased the abundance of *Bacteroides* .[64] Different types of DF support specific microbial subgroups, which may indicate that the selected fibers have the potential to achieve the target function, immune outcomes, and metabolism.[180] For example, administration of high straight-chain maize type 2 resistant starch (RS, 40 g/day) to patients with Non-alcoholic fatty liver disease for 4 months resulted in a 9.08% absolute reduction in intrahepatic triglyceride (IHTC) content, and a 5.89% reduction adjusted for weight loss factors, as a result of the RS intervention, relative to the control group (CS, given the same energy-supplied control starch). Serum branched-chain amino acids (BCAAs) and intestinal microbial species, especially *Bacteroides stercoris*, were significantly associated with IHTC and liver enzymes and were reduced by RS.[53]

Therefore, the precise use of DF interventions to achieve personalized nutrition in terms of targeted manipulation of the intestinal microbiota and its metabolic functions to promote immune health is yet to be studied in greater depth.

However, traditional recommendations for dietary interventions are usually based on populations by age and gender. It is well known that diversity in social status, culture, lifestyle, and genetic variation can influence the response to nutritional interventions. Therefore, precision nutrition is advocated as an individual nutrition program designed to treat or prevent various diseases.[181] Precision and personalized nutrition methods interfere with health by using human variability to design specific diet programs. Precision nutrition integrates the clues of behavioral, socio-cultural, physiopathological, metabolomic, macrogenomic, and genetic to understand metabolism and human health and implement healthy actions.[182] In the area of nutrigenomics, macrogenomics, which focuses on the study of intestinal microflora, has received extensive attention in recent years. As shown in Figure 5, "Big data" combines metagenomic sequencing with

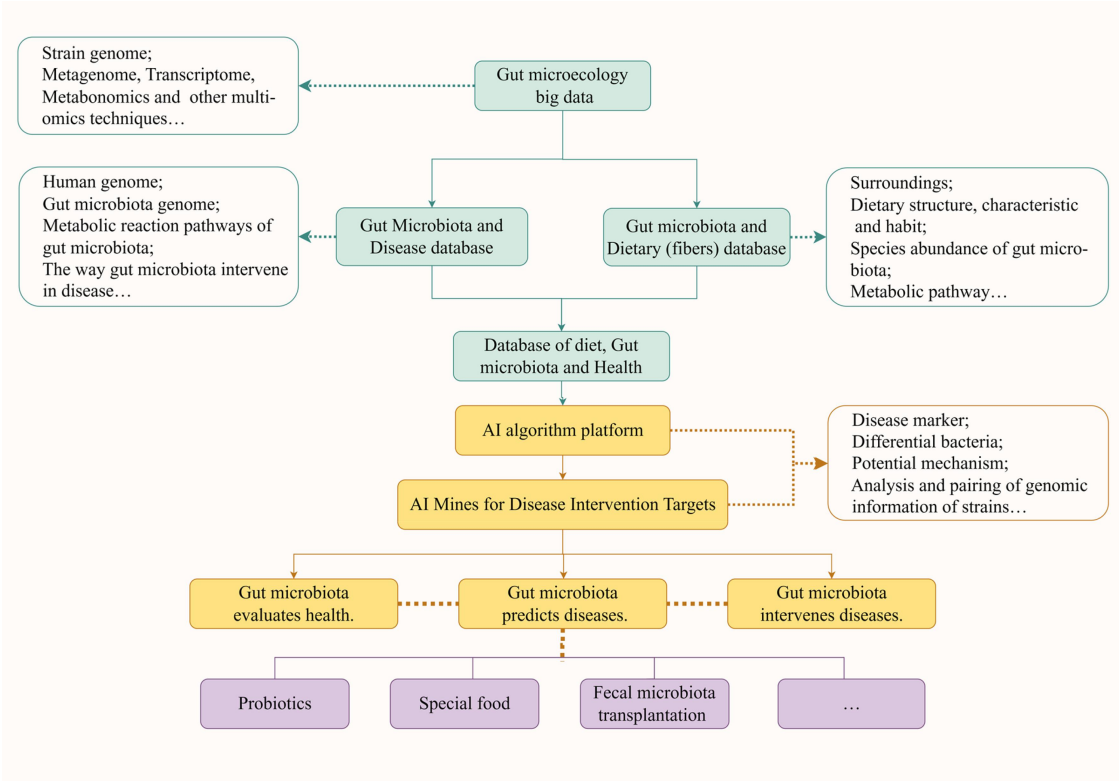

Figure 5. Precision nutrition. Backed by gut microecology big data established by strain genes, metagenome, transcriptomes, metabonomics, and other multi-omics testing technologies. To build a database of intestinal microbiota and diseases with data related to human genomes, gut microbiota genomes, metabolic response pathways of microbiota, and the way microbiota intervene in diseases. At the same time, concerning the living surroundings, customs, and other factors, we will collect data on various dietary structures, dietary characteristics, as well as changes in the abundance of microbiota species and metabolic pathways under different dietary habits, to build a database on gut microbiota, and diets. Integrate the two types of databases to build a dietary, gut microbiota, and health database. With the help of the AI algorithm platform, analyze the disease markers, find the different bacteria, analyze and compare the genes, metabolism, and other related information of the different bacteria in the database, and dig out the relevant targets of the intestinal microbiota to intervene in the disease. In turn, we will realize the functions of health assessment, disease prediction, and disease intervention, and participate in the development of probiotic preparations, special foods, and fecal transplantation technology to further realize precision nutrition.

other histologies to accurately interpret metagenomic sequencing information.[181] More and more studies show that the microbiome potentially influences human physiology through its involvement in digestion, nutrient absorption, the formation of mucosal immune responses, and the synthesis or regulation of a large number of potentially bioactive compounds. Therefore, dietary-induced microbial changes can be utilized to induce host physiological changes such as the occurrence and progress of diseases.[183] The personalized nutrition method aims to identify key microbial characteristics and predict the response to specific food components, informing diet design for favorable outcomes. A major challenge to the potential of personalized nutrition using microbiome information is to determine how the host, microbiome, and diet interact to form a dietary response.[183]

6. Conclusion

There are numerous examples of the intestinal microbiota using DF to produce metabolites that affect individual health. Intestinal microbiota affects obesity, immunocompetence, and even cancer, and is implicated in almost every major metabolic chronic disease, and DF can be targeted to manipulate the gut microbiota. Previous research has leaned more toward the relationship between

dietary patterns and health. However, we have to realize that there is a great deal of variability in response among all individuals. It may be due to our microbiota or genes, resulting in biologically different responses to the same food, the same nutrients, and the same food pattern. In this sense, precision nutrition has been unanimously proposed and a high degree of consensus has emerged. The hotspots and focuses of the scientific frontiers have also changed from the issuance of a nutritional dietary guideline for the population to guide scientific diets to the formulation of nutritional dietary guidelines for different special populations, to the provision of life-cycle, real-time, and online precision nutritional services for each individual.

To achieve this goal, it is vital to study the nutritional needs and health databases of different populations and even different individuals, to conduct more comprehensive research on the genetic information, metabolic mechanisms, and signaling of the intestinal microbiota, and to conduct a census of DF and even of the ingredients themselves, to build up a large database that can be fully evaluated from the nutritional and health perspectives.

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